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Relationship between End-Tidal CO₂ (ETCO₂) and Lactate and their Role in Predicting Hospital Mortality in Critically Ill Trauma Patients; A Cohort Study

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► ABSTRACT

Objective: To investigate the relationship between end-tidal CO₂ (ETCO₂) and serum lactate and their predictive role in hospital mortality of intubated multiple trauma patients.

Methods: In a cohort study, intubated multiple trauma patients who referred to the emergency department for two years were enrolled. After orotracheal intubation using Rapid Sequence Intubation (RSI) method, ETCO₂ was immediately measured by capnography. Blood samples for serum lactate measurements were sent to the laboratory, immediately after intubation. Data collection was done using the questionnaire, and the patients were followed using their medical records.

Results: Totally, 250 patients were included with hospital mortality of 14.8% (n=37). Using Pearson correlation, an inverse relationship was noticed between serum lactate and ETCO₂, immediately ($p < 0.0001$, $r = -0.65$). In adjusted multivariate analysis, three variables including heart rate (HR), serum lactate and ETCO₂ showed a significant relationship with hospital mortality, respectively ($p = 0.007$, $p = 0.009$, $p = 0.023$, respectively). Receiver operating characteristic curve illustrated an area under the curve (AUC) of 0.93, 0.96, and 0.97 for HR, lactate, and ETCO₂, respectively.

Conclusion: ETCO₂ post-intubation and serum lactate may be considered as prognostic factors for intubated multiple trauma patients referring to the emergency department, which can give the clinician an important clue in early prediction of the hospital mortality.

Keywords: Capnography; Hospital mortality; Lactate; Multiple trauma.

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Multiple trauma is considered as a universal health concern and it can be a threat to the patient survival rate. The term refers to the life-threatening injuries in single or multiple organs with Injury Severity Score (ISS) greater than 16, which is considered as one of the main causes of hospital mortality [1-3]. Eighty percent of hospital mortalities for multiple trauma patients occur in the first 4 hours of arrival to the emergency department. Therefore, early diagnosis and appropriate management in the emergency departments are very important [4]. Metabolic and physiologic factors may have a good predictive value in these circumstances. Multiple scoring systems, along with traditional vital signs, are helpful in determining the patient's outcomes [1-4]. One of these measurements is the non-invasive end-tidal CO₂ (ETCO₂) measurement used along with capnography. ETCO₂ is the maximum concentration of carbon dioxide at the end of exhalation, which is in direct relationship with the cardiac output [5].

The decrease occurred in cardiac output and inducing hemodynamic instability leads to the decline in the pulmonary blood circulation and ETCO₂. An increase in tissue perfusion increases the ETCO₂. This is a valuable measure to assess patients' metabolic condition. ETCO₂ is inversely related to metabolic acidosis, although there is only a moderate correlation between PCO₂ and ETCO₂ levels [6, 7]. Therefore, the use of ETCO₂ may have the prognostic role in determining the hospital mortality in the emergency department, although this role is unclear in patients with multiple trauma [8-11]. In patients with acute conditions such as trauma, with multifactorial causes and different mechanisms, serum lactate levels increase. Considering that the normal vital signs cannot rule out hypoperfusion and shock, elevating serum lactate levels can suggest tissue hypoperfusion [12]. Serum lactate is a low cost, fast, and simple test that can predict the severity of damage and mortality in multiple trauma patients [13]. While there is an inverse relationship between ETCO₂ and serum lactate in patients with suspected sepsis [14, 15], this association is unclear in intubated multiple trauma patients. The aim of this study was to investigate the relationship between ETCO₂ and serum lactate and their predictive role in hospital mortality of intubated multiple trauma patients.

Materials and Methods

Study Population

This prospective cohort study was conducted on intubated multiple trauma patients who were admitted in the emergency department of Bahonar Academic Hospital, Level II Trauma Center, affiliated to Kerman University of Medical Sciences, Kerman, southeastern Iran. All intubated multiple trauma patients with ISS \geq 16 and older than 18 years

old from March 1st, 2016 to March 1st, 2018 were enrolled. Upon arrival at the emergency department, all patients were triaged by a nurse. Non-intubated patients with an ISS $<$ 16, who aged less than 18 years old, patients with delayed arrival after an hour, patients who had died before entering the hospital, those patients who had been intubated prior to their admission to the hospital were excluded from the study. Furthermore; those patients who were pregnant, patients with a history of the chronic pulmonary disease, patients with drug and alcohol poisoning, seizure, organs failure, sepsis and also patients who were intubated through RSI method using different drugs were also excluded from the study. This study was based on the Helsinki Statement of 1975, which was revised in 1989 in Hong Kong and it was approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (IR.KMU.REC.1396.1530). Written, informed consent was taken from all patients before the study and all information remained confidential with the researcher.

Study Protocol

Patients on the 1st and 2nd triage levels were transferred immediately to the resuscitation room and were visited by a post-graduate 3rd year (senior resident). Patients would be evaluated according to the Advanced Trauma Life Support (ATLS) guideline, and if necessary, an appropriate airway was provided through orotracheal intubation using the *Rapid Sequence Intubation* (RSI) method based on an identical protocol for all patients to avoid random measurement error. Immediately after intubation, ETCO₂ was checked by sidestream capnography (IRMA CO₂ Probe). Immediately after intubation, blood samples were sent to the laboratory for measurement of serum lactate in tubes containing EDTA and lactate oxidase enzyme method was applied for biochemical analysis using the mindray device. Other variables such as age, sex, vital signs, Arterial Blood Gas (ABG), Injury Severity Score (ISS) and Revised Trauma Score (RTS) were recorded by a senior resident in a pre-prepared questionnaire for patients. The hospital mortality rate as an outcome for these patients was investigated by using medical records.

Statistical Analysis

For quantitative variables, mean \pm SD were used and for qualitative variables, the percentage of frequency was applied. To review the relationship between serum lactate and ETCO₂, Pearson correlation was used. To express the severity of the association, the Odds Ratio (OR) and Confidence Interval (CI) 95% were employed. First, univariate analysis was applied to find statistically significant associations. Then for variables with $p<0.25$, multivariate analysis with a logistic regression model to find a significant correlation was used ($p<0.05$) [16]. Finally, for

Variables that had a significant relationship with the outcome, Receiver Operating Characteristic (ROC) curve was designed. Statistical analysis was done by SPSS software (version 20, Chicago, IL, USA).

Results

Among 1490 multiple trauma patients admitted to the emergency department, 1240 patients were excluded from the study and 250 patients (male 73.6 % and female 26.4 %) were enrolled in the study (Figure 1). Hospital mortality was reported to be 37 patients (14.8 %). The mean age was 34.18±14.77

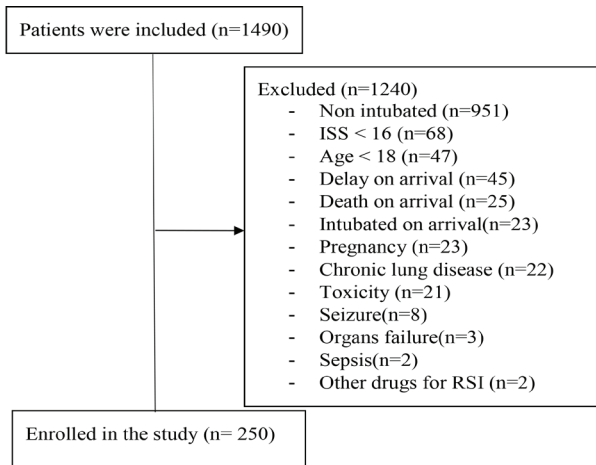


Fig. 1. Flow chart showing enrollment of patients.

Table 1. Baseline characteristics of the patients.

Variables	N (%)
Age (Years), mean±SD	34.18±14.77
Gender	
Male	184 (73.6)
Female	66 (26.4)
HR ^a (Beats/min), mean±SD	96.68±23.02
SBP ^b (mmHg), mean±SD	115.81±18.87
Lactate (meq/Lit), mean±SD	13.99±8.66
ETCO ₂ ^c , mean±SD	33.71±7.32
Hospital mortality	37 (14.8)

^aHR: Heart rate; ^bSBP: Systolic blood pressure; ^cETCO₂: End tidal CO₂

Table 2. Associations with hospital mortality using univariate regression analysis.

Variable	Mortality			
	Yes	No	OR (95% CI)	P value
Age (Years)	33.86±19.06	34.23±13.94	0.94 (0.79-1.10)	0.55
HR ^a (Beats/min)	132.16±17.64	90.48±17.62	1.12 (0.98-1.28)	<0.0001
SBP ^b (mmHg)	91.02±21.09	120.06±14.80	1.04 (0.95-1.14)	<0.0001
Base Excess (meq/Lit)	-9.69±4.44	-0.89±7.34	1.00 (0.69-1.48)	<0.0001
Hemoglobin (g/dL)	10.53±1.61	13.96±9.07	1.01 (0.69-1.48)	0.021
INR ^c	1.80±1.49	1.13±0.38	0.54 (0.15-0.00)	<0.0001
Blood sugar (mg/dL)	164.60±57.33	113.14±36.33	1.00 (0.91-1.09)	<0.0001
Lactate (mmol/Lit)	29.30±6.60	11.43±5.90	1.34 (0.87-2.05)	<0.0001
ETCO ₂ ^d	19.59±8.09	36.16±3.32	0.57 (0.26-1.26)	<0.0001
RTS ^e	4.54±1.52	7.09±0.78	0.17 (0.01-1.75)	<0.0001
ISS ^f	36.44±5.77	25.38±5.24	1.10 (0.77-1.55)	<0.0001

^aHR: Heart rate; ^bSBP: Systolic Blood Pressure; ^cINR: International Normalized Ratio; ^dETCO₂: End Tidal CO₂; ^eRTS: Revised Trauma Score; ^fISS: Injury Severity Score

(Table 1). In the Pearson correlation, there was a significant inverse relationship between serum lactate and ETCO₂ immediately ($p<0.0001$, $r=-0.65$). That is, with increasing serum lactate, ETCO₂ decreased and as it decreased, the ETCO₂ increased (Figures 2 and 3).

Then, univariate regression analysis was done. All variables except age and gender ($p=0.55$, $p=0.36$, respectively) had a significant correlation with hospital mortality (Table 2). In the multivariate analysis with the forward conditional method, three variables including heart rate (HR), serum lactate, and ETCO₂ post-intubation remained in the final

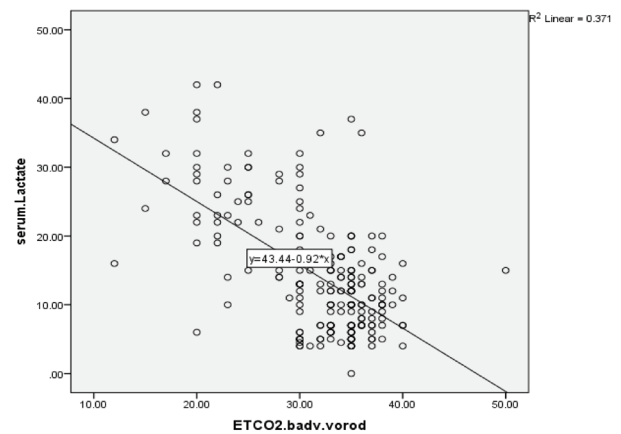


Fig. 2. Correlation of ETCO₂ on arrival and lactate concentration.

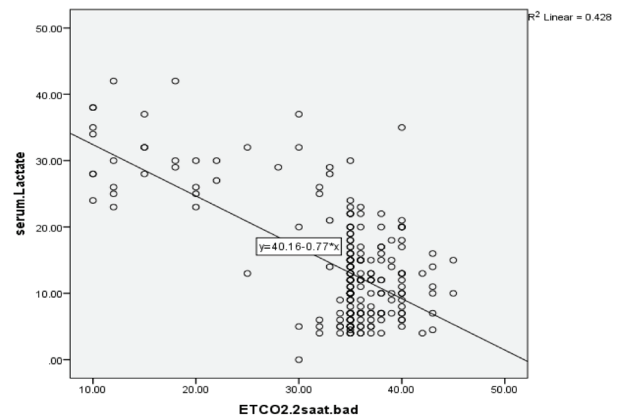


Fig. 3. Correlation of ETCO₂ 2 hours after arrival and lactate concentration.

model ($p=0.007$, $p=0.009$, $p=0.023$, respectively) had a significant relationship with hospital mortality. For each unit decrease in $ETCO_2$ and for each unit increase in heart rate and lactate, hospital mortality increased by 13%, 3%, and 26%, respectively (Table 3). For variables that had a significant statistical correlation with the hospital mortality, a Receiver Operating Characteristic (ROC) curve was drawn. The Area Under Curve (AUC) for three variables including HR, lactate, and $ETCO_2$ post-intubation were equal to 0.93, 0.96, 0.97, respectively (Table 4, Figures 4 and 5).

Discussion

While there is an inverse relationship between $ETCO_2$ and serum lactate in patients with suspected sepsis [14, 15], this correlation is unclear in intubated multiple trauma patients for determining their prognosis. However, our study showed that there was a reverse relationship between $ETCO_2$ and serum lactate in these patients. $ETCO_2$ post-intubation and serum lactate both have a predictive role in the hospital mortality in intubated multiple trauma patients. In the emergency department, the differentiation of patients with minor trauma from

the major is very difficult and the traditional vital signs are not very helpful for this differentiation [17].

One way to evaluate these patients is to examine their physiological status by measuring $ETCO_2$. Capnography is easily accessible in emergency departments and is very easy to perform. In intubated patients, capnography is performed using sidestream method by connecting the interface between the tracheal tube and the mechanical ventilation device [18]. $ETCO_2$ represents the body's perfusion so that its reduction is proportional to hypoperfusion [19]. In addition, it can also give a physician an important clue about patients' body acidity [20].

The decrease in $ETCO_2$ of patients suggests an ominous condition and can predict hospital mortality in patients [20, 21]. Therefore, $ETCO_2$ can be helpful in determining the survival rate of patients. This prognostic value has been investigated in some circumstances, such as the confirmation of the presence of an appropriate airway, the confirmation of the return of spontaneous circulation in Cardiopulmonary Resuscitation (CPR), hemodynamic instability, shock and sepsis, and evaluation during surgery [8, 21-23].

According to our experience, no study has ever

Table 3. Associations with hospital mortality using multivariate regression analysis.

Variable	OR ^a (95% CI)	P value
Heart rate	1.03 (1.01-1.06)	0.007
Lactate	1.26 (1.06-1.51)	0.009
$ETCO_2$ ^b	0.87 (0.78-0.98)	0.023

^aOR: Odds Ratio; ^b $ETCO_2$: End-Tidal CO_2

Table 4. AUC, Sensitivity, and specificity of variables from the final model.

Variable	AUC ^a	Sensitivity (%)	Specificity (%)
HR ^b	0.93	97	81
Lactate	0.96	93	97
$ETCO_2$ ^c	0.97	85	97

^aAUC: Area Under Curve; ^bHR: Heart Rate; ^c $ETCO_2$: End-Tidal CO_2

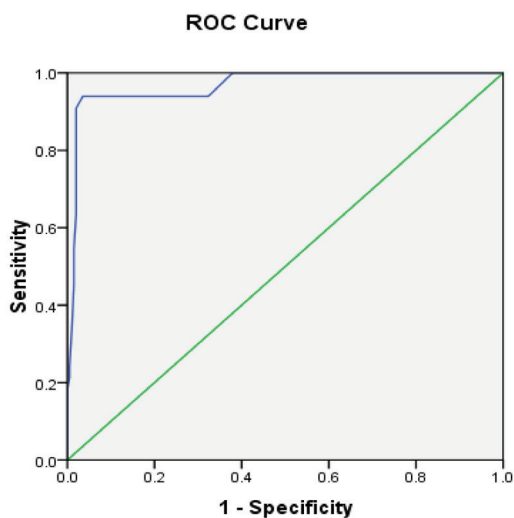


Fig. 4. Receiver operating characteristic curve for lactate predicting hospital mortality.

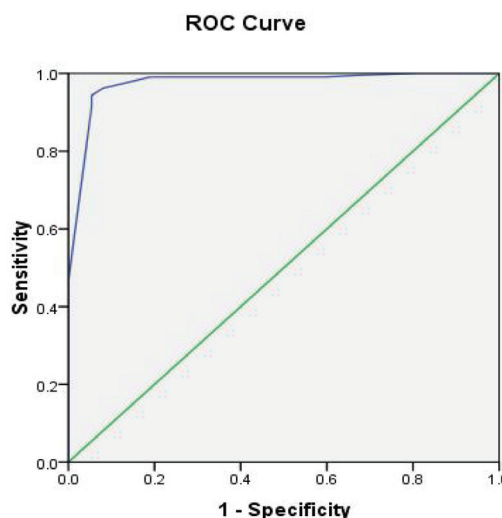


Fig. 5. Receiver operating characteristic curve for $ETCO_2$ predicting hospital mortality.

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evaluated the relationship between ETCO₂ and serum lactate in intubated multiple trauma patients in order to determine the prognosis of these patients. In this study, we observed that evaluating ETCO₂ in immediately post-intubation can have a prognostic role in predicting hospital mortality. The evaluation of serum lactate level is one of the laboratory tests that help determining the prognosis of critically ill patients. It increases under the condition of anaerobic metabolism [14, 15]. This test also increases in trauma patients, which has a direct relationship with hospital mortality [24-27]. Our study, which was conducted on intubated multiple trauma patients, also confirmed this relationship. Carbon dioxide is the product of aerobic metabolism and lactate is the product of anaerobic metabolism. By increasing serum lactate level, the patient experiences lactic acidosis. Furthermore, patients with rapid and deep breathing attempt to compensate for acidosis which results in develops respiratory alkalosis. Therefore, in critically ill patients with a severe reduction in the aerobic metabolism and increase in anaerobic metabolism, ETCO₂ decreases and lactate levels increase and it is expected that there is a significant reverse relationship between lactate and ETCO₂ [22, 28].

This relationship is helpful in determining the prognosis of these patients, which our study also confirmed this result in intubated multiple trauma patients.

There were several limitations in this study. One of the limitations was the fact that this study was a unicenter study. Non-intubated trauma patients who were less than 18 years old and patients with ISS<16, and pregnant patients were excluded from the study. Those patients who were referred from other hospitals and were late upon their arrivals, and had a chronic pulmonary illness or had drug poisoning were excluded from the study. It was not possible to measure serum lactate at all times. Patients used a different drug prescription in the RSI protocols were excluded from the study.

In conclusion, physiological and metabolic investigations can be helpful in determining the prognosis of critically ill patients. There is a reverse relationship between ETCO₂ and serum lactate in intubated multiple trauma patients. Both ETCO₂ and serum lactate have a predictive role in determining the hospital mortality in these patients.

Conflict of Interest: None declared.

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